PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference GMW/G21256WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP 03/06389	International filing date *(day/month/year)* 22.05.2003	Priority date *(day/month/year)* 24.05.2002
International Patent Classification (IPC) or both national classification and IPC C07D231/12		
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.07.2003	17.09.2004
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP 03/06389

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-532 as originally filed

Claims, Numbers

1-33 as originally filed

Drawings, Sheets

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-16 (all partly), 18, 19-31 (all partly), 32, 33

   because:

   ☒ the said international application, or the said claims Nos. 28 (as regards industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-16 (all partly), 18, 19-31 (all partly), 32, 33

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	17
	No:	Claims	1-16, 19-31
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17, 19-31
Industrial applicability (IA)	Yes:	Claims	1-16 (all partly), 17, 19-27 (all partly), 29-31 (all partly)
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

(A) Present compound **claims 1-16** relate to an extremely large number of possible compounds (see, in particular, the non-limitative (open-ended) expressions, such as "a ring optionally having 1 to 3 substituents", "optionally substituted hydrocarbon group", "hydroxy-protecting group", "optionally substituted heterocyclic ring"...etc.).
Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed.
Hence, the International Search Report (ISR) had been limited to those parts of **claims 1-16** relating to the compounds
wherein

the *ring A* is an (optionally substituted) benzene, pyridine, or pyridazine ring (cf., the present claim 3),
the *ring B* is either an (optionally substituted) pyrazol-4-yl or isoxazol-5-yl (4-yl and 5-yl in respect of the group -Xa-Ya-Xb-Yb),
the groups *Xa* and *Yb* represent bonds (cf., the present claims 12 and 14),
the group *Xb* is either a bond or a -O- group,
the group *Ya* is C_{1-6} alkylene or C_{2-6} alkenylene (cf., the present claim 7),
the group *Xc* is a bond or a -O- group (cf., the present claim 15),
the group *Yc* is C_{1-6} alkylene or C_{2-6} alkenylene (cf., the present claim 16),
the group *R* represents $-OR^4$ (cf., the present claim 11), and
the *ring C* is an (optionally substituted) monocyclic aromatic ring as defined in the present claim 1.

(B) The expression "prodrug" as used in the present **claims 18-24** and **27-30** is unclear in the sense of Article 6 PCT (this expression does not comprise any information as regards the structure of the compounds concerned).
Accordingly, the present **claim 18** had not been searched.
Claims 19-24 and **27-30** had only been searched as far as the compounds as defined under (A) are concerned.

(C) Furthermore, the initial phase of the novelty-search on the intermediate compounds of the present **claim 33** revealed such a vast number of novelty-destroying documents (cf., for example, the last five documents of the ISR) that **no** search had been carried out for the said **claim 33** (and **claim 32** which is directed to a process for the preparation of the compounds of claim 33 wherein R^{13a} represents CH_2OH).

(D) As the ISR forms the basis of this International Preliminary Examination Report, the following statement on the patentability of the present subject-matter can only be regarded as being complete in respect of the present **claim 17** (the present claims 1-16 and 19-31 have only been examined as far as the compounds as defined under (A) are concerned; beyond that only the (whole) content of the documents **D1** - **D8** and **D10** as cited in the ISR has been taken into consideration).

(E) In so far as the following letter refers to claims 1-16 and 19-31 it should only be taken to refer to the searched scope of these claims as defined in points A/D.

(F) Pursuant to Article 34(4)(a)(i) and Rule 67.1(iv) no comment is given on the question of industrial applicability of the present **claim 28**.
For the assessment of the aforesaid claim on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents (D) are considered to be relevant:

D1: ..... EP-A-1216980 (published on 26 June 2002) & WO-A-01/25181 (published on 12 April 2001);
D2: EP-A-0513580;
D3: EP-A-0378755;
D4: WO-A-96/35669;
D5: EP-A-0581095;
D6: EP-A-0525516;
D7: EP-A-0558062;
D8: EP-A-0442448;
D9: WO-A-03/015771;
D10: WO-A-00/64876;
D11: WO-A-01/38325;
D12: WO-A-01/00603;
D13: WO-A-97/31907;

The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document.
If it later turns out that this is not correct, the document **D9** could become relevant.

1. NOVELTY (Article 33(2) PCT):

The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of **claims 1-16** and **19-31** is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT):

There are overlaps between the ranges of compounds disclosed in the prior art **D1** (cf., claim 1 therein), **D2** (cf., claim 1 therein), **D3** (cf., claims 1 and 3 therein), **D4** (cf., claim 1 therein), **D5** (cf., claims 1 and 10-13 therein), **D6** (cf., claim 1 therein) and **D7** (cf., claim 1 therein) and the compounds of the present **claims 1-16**.
Moreover, **D1** (see, for instance, the compound of the example 205b, which is novelty-destroying in respect of the present claims 1-3, 5-7, 9, 11, 14, and 15), **D2** (see, for instance, the compounds 46, 99-102, and 164 on pages 168-184 which are novelty-destroying in respect of the present claims 1-3, 5-7, 9, 11, 12, and 14-16), **D3** (see, for instance, the compound 95 on page 15, which is novelty-destroying in respect of the present claims 1-9 and 11-15), **D4** (see, for instance, the compound 07 on page 185 which is novelty-destroying in respect of the present claims 1-3, 5-7, 9, 11, 12, and 14-16), **D5** (see, for instance, the compound 142 on page 43 and the compound 58 on page 61, which are novelty-destroying in respect of the present claims 1-9 and 11-15), **D6** (see, for instance, the compound 1a.300 on page 32, which is novelty-destroying in respect of the present claims 1-3, 5-7, 9, 11, 12, 14, and 15) disclose specific compounds falling within the scope of the said overlaps.

Although **D3** (cf., claim 3), **D5** (cf., claims 10-13) and **D7** (cf., claim 1) do not disclose **specific** examples of compounds falling within the scope of the present claims the whole range of overlap has to be considered to be novelty-destroying in respect of the present compound **claims 1-16** because the said compound claims 1-16 do not define a **new technical element** (new structural feature) which would render the present compounds novel over the said compounds of **D3**, **D5** and **D7**.
[The present compounds do not possess a single new (individualised) structural feature (i.e., a specifically selected chemical residue) which would confer novelty in the sense of a *novel selection*. On the contrary, the said claims of the prior art **D3, D5** and **D7** could be considered to represent novel selection *from the compounds of the present claim 1* (cf., e.g., the *2-vinyl-phenylacetic acid methyl ester* derivatives of claim 3 of **D3**, the *2-oxy-phenylacetic acid* derivatives of claim 12 of **D5** and the *phenoxyacetic acid* derivatives of claim 1 of **D7** and the definitions of "ring C", Xc, Yc, and R according to the present claim 1).]

The compounds of the present independent compound **claims 1, 24, 27** and **30** fall within the scope of claim 1 of document **D10**.
However, as **D10** does not specifically refer to compounds wherein a *ring* (cf., the present ring A) is *directly* bound to a *1,2-azole ring* (cf., the present ring B) which in turn is bound to a monocyclic aromatic ring (cf., the present ring C) via an *acyclic chain* the compounds according to the present application may be considered to represent a **novel selection** from the compounds of **D10**.
[the preferred compounds of **D10** are those wherein the Ar I ring is bound *via a linker* to the second ring Ar II, i.e., wherein either a = 1 or 2 (see, the dependent claims 3 and 6 of **D10**) or A does *not* represent a chemical bond (see, the dependent claims 4, 5, 7, 8, 23-26 and 30-38 of **D10**)]

As the compounds of **D1** are also said to be useful for the treatment of *diabetes* (cf., claim 15 therein), the present **claims 19-30** - which are directed to pharmaceutical compositions (claim 19), first medical use (claims 20-23 and 30), compounds (claims 24-27, and a method/use for the treatment of *diabetes* (claims 29 and 30) - do not satisfy the criterium of novelty either.

The documents **D2** (cf., claim 1), **D3** (cf., claims 1 and 3), **D4** (cf., claim 1), **D5** (cf., claims 1 and 10-13) and **D6** (cf., claim 1) disclose compounds with a non-medical use. However, as the present claims 24-27 and 30 are directed to *compounds* per se [as a result of the wording used (cf., for instance, claim 24: "...a retinoid-related receptor function regulating agent...") the said claims have to be regarded as compounds claims (cf., the PCT International Preliminary Examination Guidelines, 1998, chapter III-4.8 and chapter IV-7.6)], the documents **D2 - D6** are also novelty-destroying with respect to the present **claims 24-27** and **30** (it is further noted that the compounds claims 24-27 and 30 do not comprise the proviso of the present claim 1).

D7 pertains to compounds (cf., claim 1) having pharmaceutical activity (cf., claim 21 therein) and is therefore also novelty-destroying in respect of the present **claims 19-27** and **30**.

The document **D8** refers to compounds (cf., claim 2 therein) having a *medical use* (cf., claim 12: *blood platelet aggregation inhibitors*). **D8** is thus considered to be novelty-destroying with respect to the present claims **20-27** and **30** [the claims 20-23 (i) are formulated as *first medical use claims* and (ii) do not comprise the (third) proviso of the present claim 1].

The carboxylic acid derivatives of **D1** (cf., for instance, example 26e), **D2** (cf., page 16, lines 5-7), and **D7** (cf., page 18, line 12 - page 20, line 33) may be obtained by hydrolysis reaction of the corresponding esters.
Accordingly, **D1**, **D2** and **D7** are also novelty-destroying in respect of the present process **claim 31**.

2. INVENTIVE STEP (Article 33(3) PCT):

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of **claims 1-17** and **19-31** (insofar it is new; cf. item 1 above) does not involve an inventive step (Rule 65(1)(2) PCT):

(i) Given the structural features of the compounds of the prior art
- **D1** (see, the compounds of claim 1 of **D1** which differ from the compounds of the present **claim 17** essentially only in that they have a *chain other than alkyleneoxy* linking the C_{5-12} aromatic hydrocarbon group represented by Y and the C_{5-6} aromatic hydrocarbon group represented by the ring Z),
- **D10** (the compounds according to the present application represent a **selection** from the compounds of claim 1 of **D10**),
- **D11** (see, the compounds of claim 1 of **D11** which differ from the present novel compounds essentially only in that they have e.g. a *methoxybenzyl chain* rather than an *alkyleneoxy chain* linking the heterocyclic group represented by R^1 and the nitrogen-containing 5-membered hetero ring represented by the ring B),
- **D12** (see, the compounds of claim 1 of **D11** which differ from the present novel compounds essentially only in that they have an *oxazolyl* group attached to the alkyleneoxy group linker rather than an *isoxazolyl* group (cf., the definition of the present ring B), and
- **D13** (see, the compounds of claim 1 of **D12** which differ from the compounds of the present **claim 17** essentially only in that they have e.g. a *benzyl* group at the α-position of the alkanoic acid (e.g. propanoic acid) group (cf., the present divalent *aliphatic* hydrocarbon residue having 1 to 20 carbon atoms represented by Y_c), and

(ii) having regard to the fact that the compounds of **D1** (cf., page 3, line 23), **D10** (cf., claims 52 and 60), **D11** (cf., page 1, lines 5-10), **D12** (cf., page 3, lines 14-27), and **D13** (cf., page 3, lines 1-7) are also said to have *hypoglycemic* and *hypolipidemic* activity,

the solution (cf., the **novel** compounds of the present claims 1-17, 24-27 and 30) to the **problem** underlying the present application (i.e., the provision of further compounds having *hypoglycemic / hypolipidemic* action) has to be regarded as being obvious in the light of the prior art **D1** and **D10 - D13**:

The person skilled in the art *would have* ***known*** from the teaching of **D10** (cf., claims 1, 52 and 60) that compounds of the present structure would possess *hypoglycemic* and *hypolipidemic* activity (see, the present **selection** from claim 1 of **D10**).

He would have therefore expected that, for example, the *oxazole* ring of the compound of the example 23 of **D12** could be replaced by a *isoxazole* or *pyrazole* ring without impairing the *hypoglycemic* and *hypolipidemic* activity of this compound (see also, the teaching of **D1** according to which this ring (Y) may be "...a C_{5-12} aromatic hydrocarbon...which may have one or more substituents and which may have one or more heteroatoms...", **D10** according to which the corresponding ring (Ar II) may represent an (optionally substituted) "heteroaryl", **D11** where the corresponding ring (R^1) is defined as "...a heterocyclic group which may be substituted...", or **D13** where the corresponding group A stands for "...a 5- or 6-membered heterocyclic group containing at least one heteroatom selected from oxygen, nitrogen and sulfur...").

3. INDUSTRIAL APPLICABILITY (Article 33(4) PCT):

The subject-matter of **claims 1-17, 19-27** and **29-31** of the present application concerns chemical compounds (claims 1-17, 24-27 and 30), pharmaceutical compositions (claim 19), agents for use in a medical treatment (claims 20-23), the use of a chemical compound in the preparation of a medicament (claim 29) and a chemical process (claim 31) and is therefore considered to be industrial applicable in the sense of Article 33(4) PCT.

4. MISCELLANEOUS:

4.1. The document **D1** should have been cited (Rule 5.1(a)(ii) PCT).

4.2. The expressions in the claims "a ring optionally having 1 to 3 substituents", "a 1-2-azole ring optionally further having 1 to 3 substituents", "optionally substituted hydrocarbon group", "hydroxy-protecting group", "amino-protecting group", "a monocyclic aromatic ring optionally further having 1 to 3 substituents" and "an optionally substituted heterocyclic ring" are non-limitative and are therefore not regarded as obvious modifications or equivalents of the examples which have been given in the description. Accordingly, the said expressions should have been restricted in this respect to the particular meanings specified in the description (Article 6 PCT).
In this connection, it is also stressed that only those compounds which are suitable for solving the problem underlying the present application can be claimed (Article 33(3) PCT).

4.3. The term "1,2-azole ring" (cf., the present claims) is considered to be unclear (Article 6 PCT).
It is, in particular, not clear whether it exclusively refers to 1,2-azole rings such as pyrazoles, isoxazoles and isothiazoles (cf., page 35, lines 12-14) or whether it is intended to include also e.g. 1,2,3-triazoles, 1,2,4-triazoles, 1,2,4-oxadiazoles... etc..